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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,388	02/28/2002	Kevin J. Kayser	GTI-1453	6640

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Mark E. Fejer  
Gas Technology Institute  
1700 South Mount Prospect Road  
Des Plaines, IL 60018

EXAMINER

VOGEL, NANCY T

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/085,388		KAYSER ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Nancy Vogel		1636	

-- Th MAILING DATE of this communication appears n th cov r she t with the correspond nc address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____.  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input checked="" type="checkbox"/> Other: <i>Notice to comply</i> .     |

**DETAILED ACTION**

***Election/Restrictions***

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-13, drawn to a method for introducing and stabilizing heterologous and recombinant genes in a thermophilic host, classified in class 435, subclass 477.
- II. Claim 14, drawn to an integrative vector, classified in class 435, subclass 320.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used as a source of DNA for hybridization studies.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. Furthermore, especially in instances where the classifications are the same, the non-patent literature searches required for each of these inventions are not co-extensive, hence said searches would be burdensome. Therefore, restriction for examination purposes as indicated is proper.

During a telephone conversation with Atty. Mark Fejer on 10/20/03 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-13. Affirmation of this election must be made by applicant in replying to this Office action. Claim 14 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### ***Sequence compliance***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. For example, there are sequence in Table 3 that do not appear in the sequence listing. These and all sequences in the specification must be listed in the Sequence Listing and must comply with the requirements of 37 CFR 1.821-1.825.

Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Knol et al. (US Pat. No. 5,491,079).

Knol et al. disclose a method for introducing and stabilizing a heterologous gene in a thermophilic host comprising the steps of inactivating or deleting the lacZ gene in *S. thermophilus*, inserting a DNA fragment of interest into said *S. thermophilus* together with an intact lacZ gene, whereby lacZ activity in the *S. thermophilus* is restored, thereby enabling confirmation and detection of successful transformation (see Example 2, col. 12, line 10 – col. 14, line 36).

Claims 1-3, and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Kayser et al. (J. Bacteriol., Vol. 183, No. 5, pp. 1792-1795, (Mar. 2001)).

Kayser et al. disclose a method for introducing and stabilizing a heterologous gene in a thermophilic host which is *Thermus thermophilus*, comprising the steps of inactivating or deleting the malate dehydrogenase gene, inserting a DNA fragment of interest into said *T. thermophilus* together with an intact mdh gene, whereby mdh activity in the *T. thermophilus* is restored, thereby enabling confirmation and detection of successful transformation (see abstract and page 1792, first column, second paragraph – page 1795, second column). The reference teaches transformation by integration vectors ( see Fig. 2, plasmid pSJ17mdhA).

Claims 1, 3, 5, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamakoshi et al. (J. Bacteriol., Vol. 179, No. 15, pp. 4811-4814).

Tamakoshi et al. disclose a method for introducing and stabilizing a heterologous gene in a thermophilic host which is *Thermus thermophilus*, comprising the steps of inactivating or deleting the *pyrE* gene, inserting a DNA fragment of interest into said *T. thermophilus* together with an intact *pyrE* gene, whereby *pyrE* activity in the *T. thermophilus* is restored, thereby enabling confirmation and detection of successful transformation (see abstract and page 4812, col. 2, line 8 – page 4814, third paragraph.) The DNA fragment of interest is integrated into the *T. Thermophilus* DNA (see paragraph bridging pages 4813 and 4814). The reference discloses the insertion of a foreign gene, kanamycin nucleotidyltransferase, into the vector and the integration of the vector into the *T. thermophilus* genome. The reference discloses a method for producing the kanamycin nucleotidyltransferase product, by cloning the gene encoding kanamycin nucleotidyltransferase product into a multiple cloning site, downstream of a *Thermus* promoter which is the *pyrE* promoter on an integration plasmid, whereby expression of said gene is enabled, transforming a *Thermus* strain with said plasmid and expressing said gene in said *Thermus* strain using said *Thermus* promoter (see page 4814, first col., second complete paragraph).

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Mollet et al. (J. Bacteriol., Vol. 175, No. 14, pp. 4315-4324).

Mollet et al. disclose a method for introducing and stabilizing a heterologous gene in a thermophilic host which is *Streptococcus thermophilus*, comprising the steps of deleting the *lacZ* gene, inserting a DNA fragment of interest into said *S. thermophilus* together with an intact gene, whereby *lacZ* activity in the *S. thermophilus* is restored, thereby enabling confirmation and detection of successful transformation (see abstract and page 4318, first column, line 20 – page 4320, second column, last line). The DNA fragment of interest is integrated into the *S. thermophilus* DNA (see page 4320, second column, third complete paragraph). The reference discloses the insertion of a foreign gene, kanamycin nucleotidyltransferase, into the vector and the integration of the vector into the *T. thermophilus* genome.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to



consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 8, 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamakashi et al. ((J. Bacteriol., Vol. 179, No. 15, pp. 4811-4814). in view of Peredultchuk et al. (US Pat. No. 6,344,327).

Tamakashi et al. is cited essentially for the reasons set forth above.

The difference between the reference and the instant claims is that in the method for introducing and stabilizing heterologous and recombinant genes in a *T. thermophilus* host, the gene which is inactivated or deleted in said host, and which is then inserted into said modified *T. thermophilic* host, is the beta-galactosidase gene (claims 1,3, 5, and 8), and in the method of producing biotechnology products, the *Thermus* strain contains an inactivated or deleted *T. thermophilus* beta-galactosidase gene, and the plasmid used in the method, contains an intact *T. thermophilus* beta-galactosidase gene.

However, Peredultchuk et al. disclose the *T. thermophilus* beta-galactosidase gene (see column 7, lines 58-67).

It would have been obvious to one of ordinary skill in the art to substitute the *T. thermophilus* beta-galactosidase gene for the *pyr E* gene in the method disclosed by Tamakashi et al., since Tamakashi et al. disclosed that the *pyr E* gene is used as a selective marker in the disclosed methods, and since Perdultchuk et al. disclose that any marker gene can be used in expression systems for *T. thermophilus* (see col. 9, lines 1-58). One would have motivated to utilize the known *T. thermophilus lacZ* gene

in the methods of Tamakashi et al. as a selective marker in order to obtain the known property of growth on selective media, or presence of lac Z enzyme activity, to indicate the presence of a transformant containing the lac Z gene. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 3, 5, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamakashi et al. ((J. Bacteriol., Vol. 179, No. 15, pp. 4811-4814). in view of Nishiyama et al. (J. Biol. Chem., 261 (30), pp. 14178-14183).

Tamakashi et al. is cited essentially for the reasons set forth above.

The difference between the reference and the instant claims is that in the method of producing biotechnology products, the *Thermus* strain contains an inactivated or deleted *T. thermophilus* malate dehydrogenase gene, and the plasmid used in the method, contains an intact *T. thermophilus* malate dehydrogenase gene.

However, et al. Nishiyama et al. disclose the *Thermus* malate dehydrogenase gene.

It would have been obvious to one of ordinary skill in the art to substitute the *Thermus* malate dehydrogenase gene (*mdh*) for the *pyr E* gene in the method disclosed by Tamakashi et al., since Tamakashi et al. disclosed that the *pyr E* gene is used as a selective marker in the disclosed methods, and since Nishiyama et al. disclose the *Thermus mdh* gene. One would have motivated to utilize the known *Thermus mdh* gene in the methods of Tamakashi et al. as a marker in order to obtain the known

property of growth on selective media, to indicate the presence of a transformant containing the mdh gene. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods that recite the step of inactivating or deleting the phytoene dehydrogenase gene in a thermophilic host which may be *T. thermophilus*, followed by inserting a DNA fragment into said host together with an intact phytoene dehydrogenase gene from *T. thermophilus* (claim 4 and 9, and a method of producing biotechnology products which recites the use of a *Thermus* strain containing and inactivated or deleted phytoene dehydrogenase gene, and a plasmid or integration vector comprising the intact phytoene dehydrogenase gene (claim 10).

The following factors have been considered in formulating this rejection (in re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad. The nature of the invention is methods involving the use of the isolated phytoene dehydrogenase gene from thermophilic host, or from *T. thermophilus*.

An analysis of the prior art as of the effective filing date of the present application shows the lack of documentation showing the use of phytoene dehydrogenase genes from thermophilic hosts, or knowledge of the sequence thereof.

The relative skill of those in the art of genetic manipulation is high.

The area of the invention is unpredictable. It is well known that one cannot predict how to isolate any particular gene of interest, especially without some information regarding its sequence.

The present specification provides little or no guidance to support the claimed invention for a method of introducing genetic material into thermophilic species using the phytoene dehydrogenase gene as a marker. While the specification describes the isolation of the phytoene dehydrogenase gene of *T. thermophilus*, the described technique is not complete, since there is no guidance provided regarding the sequence

of primers used in the isolation process. Therefore, one could not obtain the phytoene dehydrogenase gene.

There are no working examples of a method of introducing recombinant genes into a thermophilic host using the phytoene dehydrogenase gene as a selective marker, since the disclosed example is incomplete

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to practice the claimed methods. In order to determine how to practice the claimed invention, one of skill in the art would have to design and implement the cloning of the phytoene dehydrogenase gene of thermophilic, or *T. thermophilus* microorganisms.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed method of introducing recombinant genes into a thermophilic host using the phytoene dehydrogenase gene as a selective marker.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and claim 10 and by dependence, claims 2-9 and 11-13 are vague and indefinite in the recitation of "one of inactivating and deleting" and "one of detection and confirmation" (claim 1) and "one of an inactivated and deleted characteristic gene", since it is not clear what is intended by this phrase. Presumably, "inactivating or deleting" (claim 1), and "an inactivated or a deleted characteristic gene" (claim 10) is intended, and the claims have been examined as if this was recited.

Claim 1, and by dependence, claims 2-9, are vague and indefinite in the recitation of "detection and confirmation of successful transformation using plasmid vectors and integration of said DNA fragment into a chromosome of said thermophilic host" (lines 10-11). It is not clear whether the recited "plasmid vectors and integration..." are being used somehow for the step of "detection and confirmation of successful transformation", or whether the phrase is intended to mean that confirmation of transformation takes place by restoration of the "detectable host characteristic". Clarification is required.

Claim 6 is vague and indefinite in its recitation of "CARD mutant strain", since it is not known what is meant by this term. It is noted that the term "CARD" is not mentioned in the specification.

The term "strong" in claim 10 is a relative term which renders the claim indefinite. The term "strong" is not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 10 is vague and indefinite in its recitation of the transforming step before the cloning step. Presumably, these two steps should be reversed.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (703) 308-4548. The examiner can normally be reached on 7:30 - 4:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ntv  
10/29/03



**JAMES KETTER  
PRIMARY EXAMINER**